Reply to "Reducing nonanastomotic biliary strictures in donation after circulatory death liver transplantation"

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Reply to ''Reducing Nonanastomotic Biliary Strictures in Donation After Circulatory Death Liver Transplantation: Cold Ischemia Matters''

To the Editor:

We highly appreciate the interest and the comments expressed in the letter by Gilbo et al[1] concerning our recent comparison of hypothermic oxygenated perfused versus unperfused human donated after circulatory death (DCD) livers. We have shown in this study that applying 1 to 2 hours Hypothermic Oxygenated PErfusion (HOPE) after initial cold storage protected extended DCD livers, with improved graft function and without intrahepatic cholangiopathy (IC).[2] Cold ischemia in our HOPE-treated DCD livers was, however, below 5 hours in most cases, and also 3 hours less compared with unperfused DCD livers, due to local procurement of perfused DCD grafts (median 188 minutes). The question seemed, therefore, whether the observed beneficial effect of HOPE was more related to the difference in cold ischemia, than to a true effect of HOPE.

Whereas only prospective randomized studies will provide a final answer on the benefit of machine perfusion techniques, we believe, for several reasons, that HOPE treatment was responsible for the observed effects:

First, graft survival in our study was significantly affected by HOPE treatment ($P = 0.02$), whereas it was independent from the length of cold ischemia ($P = 0.5$) in our regression analysis. The hazard ratios (HRs) for HOPE were 4.19 [95% confidence interval (CI) 0.96–18.2], and for cold ischemia 1.0 (95% CI 0.84–1.43).

Secondly, IC in unperfused DCD livers did not correlate with the length of cold ischemia, for example, none of the grafts, exposed to more than 8 hours cold ischemia, suffered from IC (Fig. 1A).

Third, several experimental transplant studies have shown a strong protective effect by end-ischemic HOPE, compared with cold storage alone, with identical cold ischemia in both groups.[3–5]

We agree with Monbaliu et al[1] that cold ischemia should be reduced as much as possible in DCD livers, as for any marginal graft. However, reliable thresholds for cold ischemia, related to irreversible IC, remain difficult to determine. Available recommendations differ between 6 and 9 hours,[6–8] depending on additional risk factors, for example, recipient LabMELD, donor age, warm ischemia during implantation, or previous liver transplantation. Most centers try to keep cold ischemia in DCD liver transplant below 8 hours. Accordingly, recent data from the United Kingdom show, in a large series of 187 DCD liver grafts, a

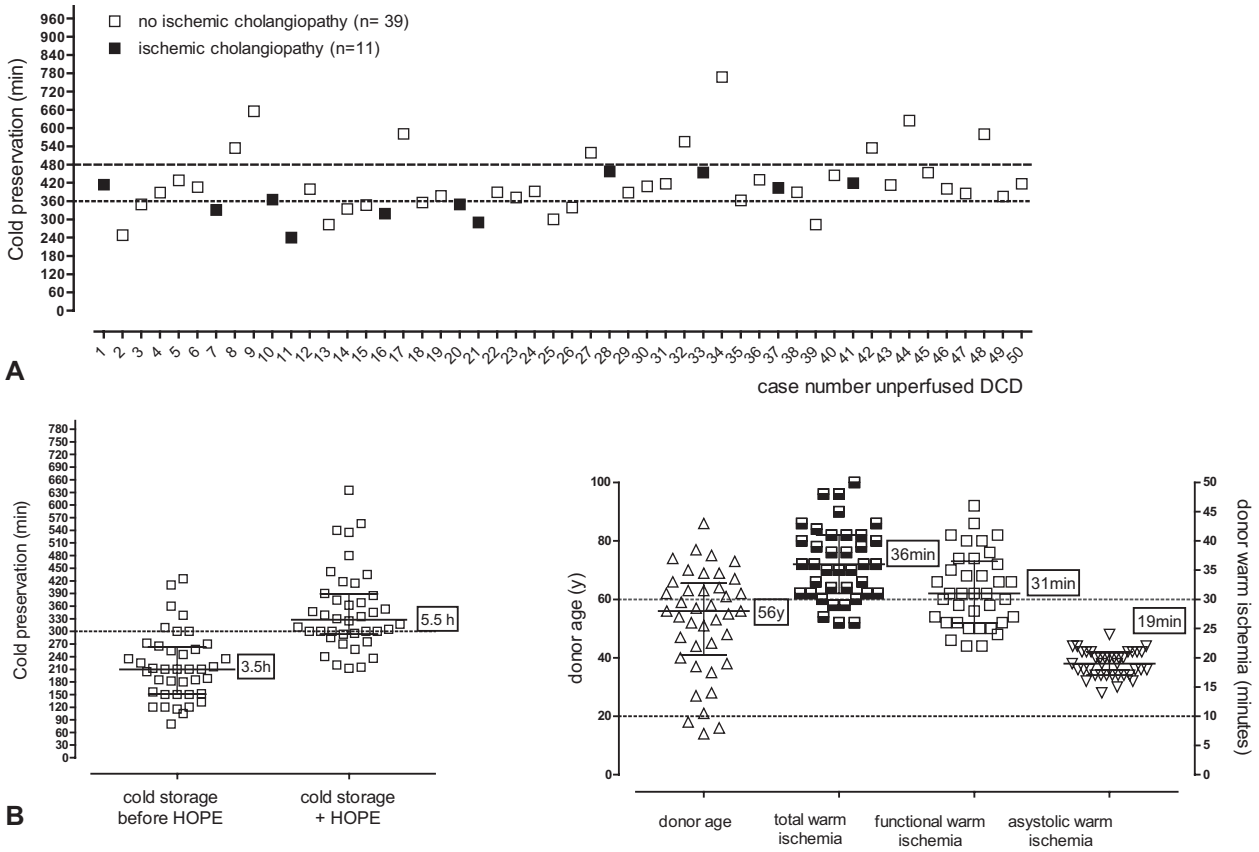

FIGURE 1. A, Negative correlation of cold preservation and ischemic cholangiopathy in unperfused DCD grafts. B, Cold and warm ischemia time in 40 machine-perfused human DCD livers (2012–2016).

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low incidence of IC (9.1%), despite a mean cold ischemia of 7.3 hours, providing that functional donor warm ischemia was kept short (mean 20 minutes).[9] These results correlate with another DCD series reporting only 2.5% IC in 167 DCD livers, exposed to a mean of 7 hours cold storage, together with functional warm ischemia of less than 20 minutes (mean 16 minutes).[10] In contrast, an increase in the asystolic to cross-clamp duration above 9 minutes is associated with a severe increase in the odds for the development of IC or hepatic necrosis by 16% per minute.[11] Based on this, it is rather unlikely that the very low incidence of IC in our HOPE-treated patients is related to short cold storage, in the presence of an extended donor warm ischemia (asystolic to cross-clamp duration 18 minutes).[2]

We have meanwhile performed 40 DCD liver perfusions with HOPE, with a median cold ischemia time of 210 minutes before HOPE, and a total cold preservation time (including HOPE) of 328 minutes (Fig. 1B). Several grafts have been exposed to longer cold ischemia with no obvious disadvantage. Functional warm ischemia and asystolic warm ischemia remain high in our center (median 31 and 19 minutes; Fig. 1B), due to our legal restriction requesting long no-touch periods and additional brain death confirmation after cardiac arrest. Despite this burden, we currently do not see IC in our HOPE-treated DCD livers, which supports, from our point of view, a clear advantage of this simple, practical, and end-ischemic perfusion approach.

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